Pharmacology, Selection and Complications Associated with Neuromuscular Blocking Drugs in ICU Patients

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INTRODUCTION

Use of neuromuscular blocking (NMB) drugs in the intensive care unit (ICU) increased dramatically in the 1980s but has decreased recently [1, 2]. Currently, it is estimated that ≤5 percent of ICU patients receive continuous administration of NMB drugs for 24 hours or more [2]. Utilization is tempered by recognition of untoward side-effects and complications associated with prolonged administration of NMB drugs [3], including NMB drug toxicity, drug-drug interactions and prolonged weakness or myopathy [4], most notably in patients with the syndromes of systemic inflammation (SIRS), acute renal failure and multiple organ dysfunction syndrome [5-12]. In addition, NMB drugs may precipitate hemodynamic, autonomic and other physiologic interactions in ICU patients.

NMB drugs are used in the ICU to facilitate mechanical ventilation, as adjunctive therapy in the control of intracranial hypertension, to eliminate shivering and decrease oxygen consumption, as supportive therapy of tetanus or status epilepticus (with EEG monitoring), to optimize conditions for certain diagnostic procedures and to facilitate endotracheal intubation [13]. Other less common (and controversial) indications are to ensure patient immobility during invasive procedures or patient transport, emergent control of agitated or combative patient, and selected patients with severe cardiovascular instability.

While all NMB drugs interact with the postjunctional nicotinic acetylcholine (nACh) receptor [14], they exhibit unique pharmacologic and clinical profiles [13]. In addition, NMB drugs vary significantly in acquisition costs [15]. The use of these drugs may constitute a large proportion of the ICU pharmacy budget. However, pharmaco-economic evaluation of ICU drug use must take into account secondary costs such as personnel requirements, use of infusion devices, long-term effects of drug and drug metabolites and potential patient morbidity or mortality secondary to side-effects of specific drugs [16].

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NMB drugs reversibly block impulse transmission at the nicotinic acetylcholine receptor (nAChR), clustered at the neuromuscular junction of skeletal muscle [17]. Historically, the nAChR was the first ion channel protein to be isolated and purified, and is classified as a transmitter, or ligand-gated channel.

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b Abbreviations: NMB, neuromuscular blocking; ICU, intensive care unit; SIRS, syndrome of systemic inflammation; nAChR, nicotinic acetylcholine receptor; TOF, train of four; CK, creatine phosphokinase; EMG, electromyography; CIP, critical illness polyneuropathy; ICP, intracranial pressure.

Nicotinic-AChR are clustered at the muscle endplate (each endplate has one to ten million receptors), concentrated on the crests of the postjunctional membrane folds. Each nAChR is a glycoprotein complex composed of five subunits, alpha, beta, epsilon, and delta in a ratio of 2:1:1:1, with each of the two alpha subunits acting as an ACh binding site [14, 17]. When simultaneously stimulated by two ACh molecules, the channel undergoes conformational change and opens for about one millisecond, allowing relatively nonselective passage of small positively charged ions, mainly sodium (Na^+, peak rate of $\geq 30,000$ ions per channel per millisecond), potassium, and some calcium. This Na^+ influx depolarizes the nearby muscle membrane, triggering local voltage-gated Na^+-channels, and thereby creates a self-propagating depolarization (i.e., an action potential). Excitation-contraction coupling occurs, and muscle contraction results. Subsequently, the nAChR channel recycles itself for the next nerve impulse.

Normal neural activity and stimulation of the motor endplate regulates the translation and membrane integration of the nAChR. Normal cholinergic neuron input is critical to clustering nAChR underneath nerve terminals and maintaining a high concentration (200,000 receptors/μm2) at the neuromuscular junction. Adult skeletal muscle retains an ability to synthesize an immature nAChR variant, in which a gamma subunit is substituted for the normal epsilon subunit (Figure 1). In diseases such as Guillain-Barré, stroke, polio, spinal cord injury, burns, severe muscle trauma, enforced immobilization, or other conditions producing loss of nerve function, synthesis of immature (fetal) receptors may be triggered. These immature nACh receptors are distinguished by three features. First, immature receptors are not localized to the muscle endplate but migrate across the entire membrane surface. Second, the immature receptors are metabolically short-lived (<24 hrs) and more ionically active, having a two- to 10-fold longer channel "open time." Lastly, these immature receptors are more sensitive to the depolarizing effects of drugs such as succinylcholine or decamethonium and more resistant to the effects of competitive antagonists such as d-tubocurarine. The clinical consequences of up-regulation of these immature receptors are profound clinically [18]. In acute spinal cord injury and
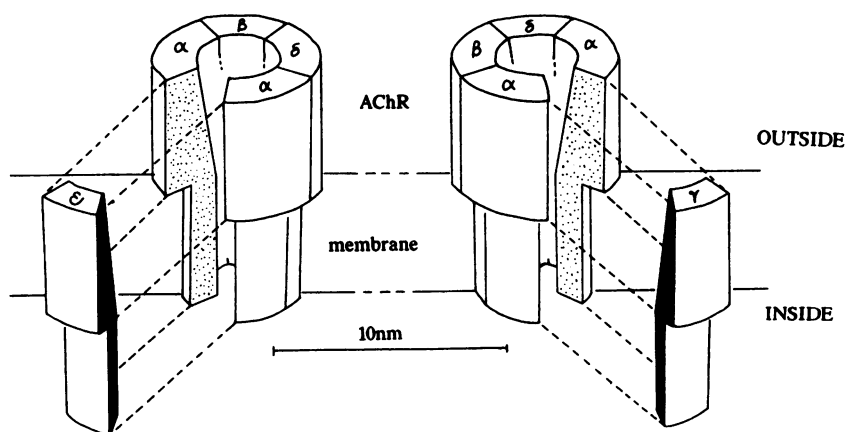

Figure 1. The mature, adult nicotinic acetylcholine receptor (left) and the immature, or fetal - variant receptor (right). These receptors differ by a single subunit substitution, which produces immature receptors characterized by ten-fold greater ionic activity, rapid metabolic turnover and extrajunctional proliferation. (Reprinted with permission from Martyn, J.A., White, D.A., Gronert, G.A., et al. Anesthesiology 76:822, 1992.)

burn patients, denervation-induced proliferation of immature gamma-subunit nACh receptors likely explains the sensitivity and potentially-lethal hyperkalemic response to depolarizing agonists like succinylcholine. In addition, this same phenomenon may explain the drug resistance and tachyphylaxis to nondepolarizing NMB drugs.

TWITCH MONITORING IN THE ICU

Neuromuscular block in the operating room is routinely monitored by qualitative grading of a motor response to transcutaneous peripheral nerve stimulation [19, 20]. In this way, neuromuscular function can be assessed independently of confounding variables such as sedation, depth of anesthesia or patient cooperation. Most authorities now universally recommend use of a hand-held peripheral nerve stimulator in the ICU to titrate the depth of neuromuscular blockade and prevent significant and unnecessary NMB drug overdose. Indeed, routine use of neuromuscular function monitoring with a peripheral nerve stimulator has been advocated to limit, if not eliminate, prolonged weakness after use of NMB drugs in the ICU [8]. While theoretically desirable, avoiding periods of profound (or complete) neuromuscular block with twitch monitoring in ICU patients cannot guarantee return of normal neuromuscular function once the NMB drug is discontinued. Traditionally, the ulnar nerve at the wrist is stimulated while evaluating the motor response of the adductor pollicis brevis muscle of the thumb [19, 20]. Other peripheral nerve sites (such as facial nerve stimulation while grading the orbicularis oculi muscle, or stimulating the peroneal nerve of the upper leg and grading foot dorsiflexion) are also feasible. Patients with strokes, paraplegia or dense peripheral neuropathies should be monitored on unaffected limbs, since affected extremities will exhibit altered responses (resistance) to neuromuscular blockade.

The train-of-four (TOF) response delivers four supramaximal stimuli (40 to 60 mA current) at 2 Hz while the motor response of the 4th twitch (T4) is compared to the twitch response of the first stimulus (T1) [19, 20]. Nondepolarizing block is characterized by a progressive decrement in each successive motor twitch response, (a TOF response of <0.7), the presence of fade during tetanic stimulation and the presence of post-tetanic facilitation (Figure 2) [19, 20]. The main shortcoming of peripheral nerve stimulation is that global muscle function is inferred from the response of a single peripheral muscle group. For instance, the diaphragm and laryngeal muscles are more resistant to neuromuscular blockade than the adductor pollicis brevis muscle and also recover more quickly after cessation of NMB drugs [21]. In some patients, a TOF count of 0 at the adductor pollicis muscle may not correlate with a level of neuromuscular block sufficient to adequately manage clinical endpoints such as elimination of coughing during suctioning, eliminate peripheral motor movements, or dyssynchrony ("triggering") of the ventilator. Thus, a TOF count of 0 does not necessarily represents a failure of monitoring or drug titration but may reflect both the difficulty of administering NMB drugs in the ICU and the need for clinical endpoints discrepant with the monitored twitch at the adductor pollicis. It is important, therefore, to utilize a combination of both peripheral nerve stimulation and clinical assessment to evaluate neuromuscular function and degree of neuromuscular blockade. Critically ill patients rarely require dense, 100 percent receptor blockade, especially when NMB drugs are accompanied by adequate delivery of sedative and analgesic drugs. NMB drugs should be titrated to the minimally effective dose, maintaining the least degree of neuromuscular block that provides optimal patient care. Regardless, a fixed level of neuromuscular block is difficult to maintain in ICU patients due to factors such as changing body temperature, alterations of muscle blood flow, altered electrolytes, use of

concomitant medications such as aminoglycosides, magnesium, calcium-channel blockers, and so forth.

NMB DRUGS AND COMPLICATIONS IN THE ICU

Use of NMB drugs in the ICU may be associated with numerous potential adverse effects (Table 1). Precautions to limit these effects include a secured, unobstructed airway, positive pressure ventilation, appropriate inspired oxygen concentration, concurrent sedation and analgesia, precautions to avoid pressure on vulnerable points of nerves, eyes, and skin, and prophylaxis for deep venous thrombosis.
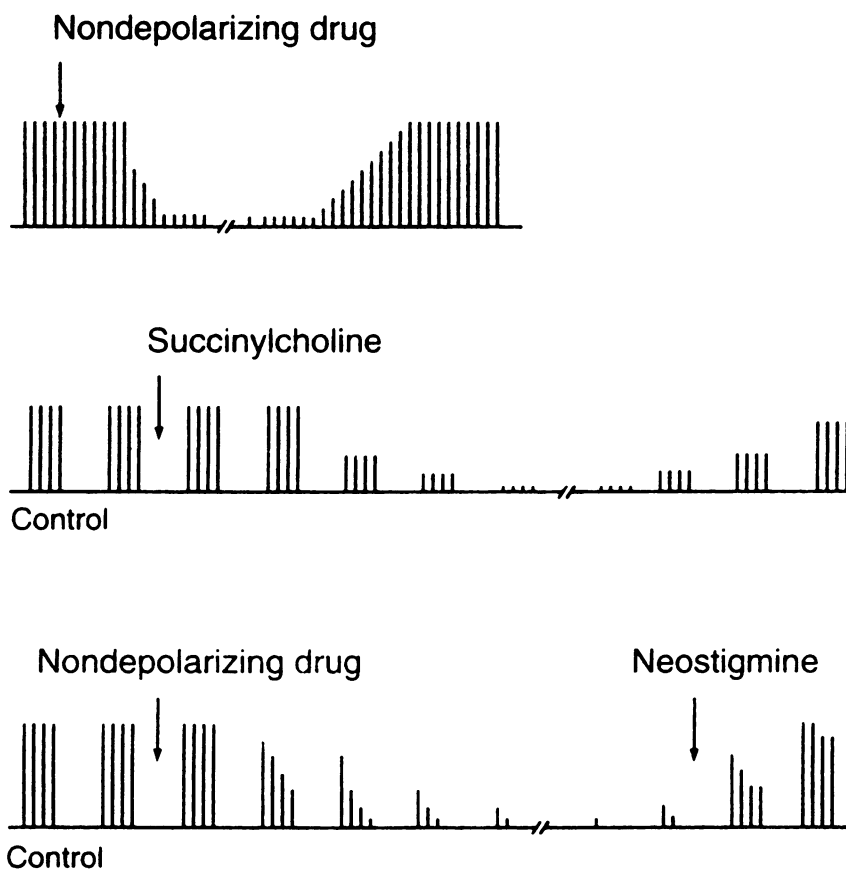

Figure 2. Top panel shows the effect of a nondepolarizing neuromuscular blocking (NMB) drug, e.g., pancuronium, on the single twitch response at 1 Hz. The middle panel shows the effect of succinylcholine (a depolarizing NMB drug) on the train-of-four (TOF) response applied at 2 Hz after a baseline period is established. Note that all four twitches are depressed equally, and that there is no fade of the response during either onset or recovery from this type of neuromuscular block. The bottom panel shows the more common effect of a nondepolarizing NMB drug producing a decrement in the TOF response ("fade"). The TOF response can be advantagous in that no baseline period is required for effective monitoring. In this case, recovery was hastened by use of the anticholinesterase drug, neostigmine. (Reprinted with permission from Hunter, J.M. N. Engl. J. Med. 332:1691, 1995.)

Table 1. Potential complications: NMB drugs in the ICU.

Complications and contraindications of succinylcholine in the ICU:
- Immediate cessation of spontaneous respiration
- Hyperkalmia due to multiple risk factors [30]
- Increased intragastric pressure
- Increased intraocular pressure
- Parasympathomimetic effects with cardiac arrhythmias
- Muscle fasiculations (myoglobinemia, especially in children)
- Potential for Phase II block

General complications associated with NMB drugs in the ICU:
- Awake, paralyzed, stressed patient
- Risk of ventilator disconnect or airway mishap
- Autonomic and cardiovascular interactions
- Tachycardia or bradycardia; hypotension or hypertension
- Accumulation of parent drug or drug metabolites
  (e.g., Laudanosine, 3-desacetylvecuronium, 3-OH-pancuronium)
- Decreased lymphatic flow, impaired respiratory clearance
- Risk of generalized deconditioning, skin breakdown
- Peripheral nerve injury
- Corneal abrasion, conjunctivitis
- Risk of prolonged muscle weakness and "postparalytic syndrome" (myopathy)
- Potential central nervous system toxicity
- Potential interactions with leukocytes
- Drug cost

Recent evidence documents unexpected complications after NMB use in the ICU, including prolonged recovery and even myopathy during or after NMB drug administration [22-24]. These adverse events may be related to the frequent use of NMB drugs, along with the mode of administration, depth of neuromuscular blockade, the specific drug administered, and NMB drug interactions. Unresolved issues include the postulated benefit of routine twitch monitoring of neuromuscular function, definition of screening tests for impending muscle injury, the alleged benefit of a "drug holiday" (whereby NMB drugs are briefly discontinued once each day to examine neuromuscular recovery), the effects of prolonged immobility, and the association of neuromuscular pathology with sepsis. These adverse effects may be divided into pharmacologic, physiologic, and toxic mechanisms (the later is the most elusive to delineate). "Prolonged recovery" in the ICU will be defined as neuromuscular recovery which requires significantly longer than expected (e.g., >120 min after discontinuation of intermediate-acting NMB drugs such as atracurium or vecuronium) based on usual and recognized pharmacokinetic parameters for NMB drugs. "Myopathy" will be defined as the clinical triad of persistent clinical paresis, increased creatine phosphokinase (CK) concentrations and abnormal electromyography (EMG) and nerve conduction studies after ICU administration of NMB drugs.

Pharmacologic

The metabolism of NMB ranges from negligible (and metocurine) to extensive (succinylcholine, vecuronium) [22-24]. Redistribution of long-acting NMB drugs is important in limiting the pharmacodynamic effects after a single bolus dose, as these drugs undergo less biotransformation and more renal excretion of unchanged drug. However, during long-term ICU administration of NMB agents, drug excretion and production of active drug metabolites are increasingly important. In the past, the steroid-based NMB drugs (pancuronium and vecuronium) were most commonly used [25, 26], which may have

contributed to the majority of case reports of prolonged weakness or myopathy being associated with these particular NMB drugs [12]. This association of an increased risk inferred by specific NMB drugs must also be critically examined in the dynamic milieu of heterogeneous ICU patients with altered drug pharmacokinetics. For instance, vecuronium undergoes hepatic hydrolysis to three metabolites: 3-des, 17-des, and 3,17 desacetylvecuronium [11, 27]. These metabolites, excreted primarily in the bile, vary in NMB activity. The 3-desacetyl metabolite is estimated to be 80 percent as potent as the parent compound, while 17- and 3,17- metabolites are far less potent. The 3-desacetylvecuronium metabolite accumulates in normal volunteers and patients in renal failure and is poorly dialyzed and minimally ultrafiltrated. Vecuronium has a three-fold increase in the elimination half-life due to an increased volume of distribution in patients receiving prolonged administration. In addition, the hepatic elimination of 3-desacetylvecuronium is decreased in patients uremic for ≥ 36 hours. The accumulation of both 3-desacetylvecuronium and vecuronium in renal failure likely contributes to prolonged weakness in this subset of ICU patients. Similarly, pancuronium is a bisquaternary NMB drug, which is desacetylated at the C3- position of the steroid nucleus to 3 desacetylpancuronium. The 3-OH metabolite is lipophilic, 90 percent bound to plasma proteins, approximately 50 percent as active as the parent pancuronium, and may accumulate in patients with renal insufficiency. The combination of decreased clearance, increased volume of distribution, and accumulation of active 3-OH-metabolites in renal failure may be a pharmacologic mechanism for prolonged weakness in some ICU patients.

Table 2. Drug-drug interactions: neuromuscular blocking (NMB) drugs.

Drugs that potentiate the action of nondepolarizing NMB drugs:
- Local anesthetics
- Lidocaine
- Antibiotics
- Aminoglycosides (gentamicin, tobramycin, amikacin)
- Polypeptides (polymyxin B)
- Other antibiotics (clindamycin, tetrcyclin)
- Antiarrhythmics
- Procainamide
- Quinidine
- Magnesium
- Calcium-channel blockers
- β-adrenergic blockers
- Chemotherapeutic agents
- Cyclophosphamide
- Dantrolene
- Diuretics
- Furosemide (biphasic response)
- Thiazides
- Lithium carbonate
- Cyclosporine

Drugs that antagonize the actions of nondepolaring NMB drugs:
- Penytoin
- Carbamazepine
- Theophylline
- Ranitidine
- Chronic exposure to nondepolarizing NMB drugs

There are a wide range of drugs with complex interactions with NMB drugs. These drug-drug interactions may either antagonize or potentiate the effect of NMB drug motor block (Table 2). Attention is focused on patients who receive both NMB drugs and exogenous corticosteroids [12, 28]. The long-term effect and potential toxicity of some of these interactions has yet to be defined, especially those not secondary to altered pharmacokinetics or dynamics.

What can be done to decrease the incidence of prolonged weakness in the ICU after NMB administration? Transcutaneous peripheral nerve stimulation may facilitate neuromuscular assessment independent of confounding ICU variables such as sedation, alterations in mental status or patient cooperation, and thereby facilitate more precise titration of NMB drug therapy. Indeed, routine use of neuromuscular function monitoring with a peripheral nerve stimulator has been advocated to limit, if not eliminate, prolonged weakness after use of NMB drugs in the ICU. Unfortunately, recent evidence does not support this hypothesis. While theoretically desirable, avoiding periods of profound (or complete) neuromuscular block with twitch monitoring in ICU patients cannot guarantee return of normal neuromuscular function once the NMB drug is discontinued. Prielipp reported the use of either vecuronium or cisatracurium (51W89) for an average of three days in 58 ICU patients. Despite the routine use of neuromuscular twitch monitoring, 15 patients demonstrated prolonged recovery, and one patient developed a profound myopathy (139 days) [29]. The reason may be certain limitations noted with peripheral nerve monitoring in the ICU. For instance, a train-of-four (TOF) count of 1 or 2 at the adductor pollicis muscle may not correlate with a level of neuromuscular block sufficient to adequately manage clinical endpoints such as elimination of coughing during suctioning, eliminate peripheral motor movements or asynchrony ("triggering") of the ventilator. For instance, in patients with critically elevated intracranial pressure, an exceptionally deep level of neuromuscular block is required to ablate the tracheal reflex to endotracheal suctioning. Thus, in certain situations in the ICU, a TOF count of 0 (at the adductor pollicis) is required, markedly decreasing the functional utility of twitch monitoring as a safeguard from excessive NMB doses.

Physiologic

Pathophysiologic changes occur at the nerve, neuromuscular junction and muscle in critically ill patients. Physiologic changes are enhanced when patients are immobilized or denervated secondary to CNS or spinal cord injury as well as during NMB drug-induced paralysis. The nAChR may be triggered to revert to a fetal variant structure, characterized by an increase in total number, frequent extrajunctional proliferation and "resistance" to nondepolarizing NMB drugs. This may account for the observations of some ICU patients developing tachyphylaxis to NMB drugs. The proliferation and distribution of these altered receptors across the myomembrane may, however, simultaneously sensitize patients to depolarizing drugs such as succinylcholine. Succinylcholine stimulation of the immature, fetal receptors allows increased cation transport, which may clinically manifest as life-threatening hyperkalemia in these patients [30].

Additional investigation and evaluation on the effect of prolonged NMB exposure to nerves, neuromuscular junctions and muscle are still ongoing. For instance, there is increasing recognition of an entity termed critical illness polyneuropathy (CIP). The sensory and motor polyneuropathy of CIP differentiates this process from other neurologic and myopathic processes encountered in the critically ill (Table 3). CIP occurs most commonly in elderly, septic patients who are severely ill for prolonged periods [31-33]. Up to 70 percent of septic ICU patients are reported to develop some elements of CIP. The process is associated with a high mortality, but if patients survive their underlying disease, they may make a full recovery. However, recovery requires a protracted period (three to

Table 3. Possible causes of weakness in ICU patients.

- Residual NMB drug effect
  - Secondary to parent drug, drug metabolite or drug-drug interaction
- Myasthenia gravis
- Eaton-Lambert syndrome
- Muscular dystrophies
- Guillian-Barré
- Central nervous system injury or lesion
- Spinal cord injury
- Steroid myopathy
- Critical illness polyneuropathy
- Disuse atrophy
- Severe electrolyte toxicity (e.g., magnesium)
- Severe electrolyte deficiency (e.g., hypophosphatemia)

six months) of hospitalization and supportive care. CIP is a diagnosis of exclusion, after examination of the clinical setting, determination of a diffuse sensorimotor deficit, and EMG and nerve conduction studies. CIP is hypothesized to be a result of primary axonal degeneration, perhaps related to microvascular ischemia of the nerve during SIRS. It does not appear to be directly related to the use of NMB drugs. It is further differentiated from Guillain Barré by the absence of inflammatory changes in nerve fibers and the presence of normal cerebrospinal fluid.

Toxic

The incidence of prolonged weakness after NMB drugs remains unknown, although Op de Coul and colleagues reported prolonged weakness (of unknown and variable) etiology in 20 percent of consecutive patients who received long-term administration of pancuronium [10]. Murray et al. prospectively monitored patients in the ICU at the Mayo Clinic and estimated the risk of clinically significant prolonged neuromuscular block was five percent [1]. The actual incidence is likely dependent on numerous factors, perhaps including the administration of various antibiotics (aminoglycosides), corticosteroids, anticonvulsants, magnesium, calcium-channel blocking drugs and other medications that may interact with NMB drugs. The incidence of true myopathy is certainly less than the occurrence of prolonged weakness in the ICU.

The direct toxicity of NMB drugs is poorly characterized and may be additive to alterations of NMB drug pharmacology discussed previously. In addition, alterations in nerve, muscle and neurotransmission may increase the toxicity of normally non-toxic drugs or drug metabolites. Concerns about untoward effects of NMB drugs in the ICU have lead some to even advocate elimination of prolonged use of NMB drugs in critically ill patients. Others have suggested that certain NMB drugs may be better suited than others in the ICU setting with renal failure, hepatic failure, NMB drug tachyphylaxis, or concurrent use of parenteral corticosteroids (e.g., for status asthmaticus, ARDS, connective tissue disease, etc). Unfortunately, much of the evidence remains anecdotal.

The acute myopathy, often referred to as "post-paralytic quadriparesis or tetraparesis" is an infrequent, but major complication after prolonged NMB administration in the critically ill. This entity must be differentiated from other neuromuscular pathologies noted above (Table 3). Afflicted patients demonstrate diffuse weakness, which persists long after the NMB drug administration is discontinued. Neurologic examination reveals primarily a global motor deficit and tends to afflict proximal and distal muscles equally. Barohn et al. described three patients with myopathy, characterized by low amplitude compound

motor action potentials, normal sensory studies and fibrillations [34]. Muscle biopsy showed loss of thick, myosin filaments. Variable increases in CK may be detected, depending on the timing of lab determinations and the initiation of the myopathic process. Thus, there may be some justification in routinely screening high risk patients with serial CK determinations during the infusion of NMB drugs. It is unclear whether drug combinations such as aminosteroid NMB drugs and concurrent administration of exogenous corticosteroids infer any specific increased risk, but is probably best avoided.

There are now a small number of reports of a myopathy developing after ICU administration of the benzylisoquinolinium NMB drugs (e.g., atracurium) [35]. We and others have diagnosed myopathy (clinical weakness, increased CK concentrations, and abnormal EMG studies) in patients after atracurium was administered for 3-4 days in the ICU. However, these patients also received corticosteroids, aminoglycosides, and one suffered chronic renal insufficiency. Myopathy occurred in both of our ICU patients despite the routine use of a peripheral nerve twitch monitor to titrate NMB drug administration.

The diagnosis of the patient with prolonged weakness, paresis, and possible myopathy after discontinuation of NMB drugs requires a systematic approach. This includes a thorough history and physical examination combined with review of recent medications and identification of related nerve or muscle pathology. First, potential residual neuromuscular blockade should be investigated with a peripheral nerve stimulator. In addition, early neurologic consultation with appropriate diagnostic examination including EMG/NCV, CK analysis, and muscle biopsy should be undertaken when indicated.

PROSPECTIVE STUDIES OF NMB DRUGS IN THE ICU

Rocuronium

Sparr reported rocuronium drug requirements for bolus administration (median dose = 0.34 mg/kg/hr) and continuous infusion (0.54 mg/kg/hr) in 32 adult ICU patients [36]. NMB drug requirements decreased during the first six to nine hours, because the $T_{1/2}{}^\beta$ (terminal half-life) and the volume of distribution at steady state increased three-fold [36]. Circeo confirmed these findings in ten adult ICU patients where the mean rocuronium infusion rate during the first four hours (8.1 µg/kg/min) decreased significantly after 24 hours (5.2 µg/kg/min) [37]. Median time for recovery to the fourth twitch in the TOF stimulation was 60 to 100 min, but recovery to the more robust 70 percent T_4/T_1 ratio was widely variable (99-1157 min) [37].

Doxacurium and pancuronium

Murray compared bolus injection of pancuronium (0.05 mg/kg) and doxacurium (0.025 mg/kg) in a double-blind, randomized study of 40 severely ill, adult patients paralyzed for two to three days in the ICU, using twitch monitoring to guide intermittent NMB drug administration [38]. Pancuronium significantly increased heart rate 11 beats per minute, whereas there was no change after doxacurium. Furthermore, neuromuscular recovery (to appearance of T_4 in the TOF stimulus) was more variable and prolonged (279 ± 229 min) after pancuronium, compared to recovery following doxacurium (138 ± 46 min) [38]. Patients who received pancuronium with concomitant renal insufficiency (creatinine clearance <50 mL/min) were most likely to exhibit prolonged recovery.

The dose requirements and neuromuscular recovery of doxacurium administered as a continuous infusion has recently been defined in adult ICU patients with head injuries [39]. Patients were paralyzed for 66 ± 12 hours (range 20 to 109.5 hours). The doxacurium infusion rate appeared similar at the beginning (1.0 ± 0.1 mg/hr) and end of the study (1.3 ± 0.4 mg/hr). Doxacurium bolus had no effect on heart rate, mean arterial pressure or

intracranial pressure. After discontinuation of doxacurium infusion, neuromuscular recovery required 118 ± 19 min (note similarity to the recovery times reported by Murray et al.). There were no complications, prolonged weakness or myopathies in this select group of patients with traumatic brain injury.

Cisatracurium and vecuronium

The dose-response and recovery pharmacodynamics of two intermediate-acting NMB drugs, cisatracurium and vecuronium, were compared in a prospective, randomized, double-blind, multicenter study in 58 critically ill adults [29]. These NMB drugs were administered as an infusion for one to five days, titrated by peripheral nerve stimulation and twitch monitoring. Cisatracurium infusion averaged 2.6 ± 0.2 $\mu g/kg^{-1}/min^{-1}$ for a mean duration of 80 ± 7 hours. Neuromuscular recovery to 70 percent TOF ratio was 63 ± 12 min. Vecuronium infusion averaged 0.9 ± 0.1 $\mu g/kg^{-1}/min^{-1}$ for a mean duration of 66 ± 12 hours. The mean time to neuromuscular recovery after vecuronium was significantly longer (387 ± 163 minutes). In addition, prolonged recovery of neuromuscular function occurred more commonly after vecuronium drug infusion (13 of 30 patients), compared to cisatracurium (two of 28 patients).

Cisatracurium and atracurium

The pharmacodynamics and pharmacokinetics of the two benzylisoquinolinium intermediate-acting NMB drugs, cisatracurium and atracurium, were examined in a prospective, randomized, double-blind, study in 12 mechanically ventilated ICU patients paralyzed for 1-2 days [40]. Neuromuscular recovery to 70 percent TOF ratio required 60 min after the cisatracurium infusion and 62 min following atracurium. Cisatracurium was 2.5 times more potent than atracurium in these ICU patients, which translated into significantly lower plasma laudanosine concentrations after cisatracurium (peak value = 1.3 $\mu g/mL$) compared to atracurium (maximum concentration = 4.4 $\mu g/mL$) [40].

Other controversies associated with NMB drugs in the ICU

NMB Drugs and Patients with Head Trauma. At least 50 percent of patients with severe head injury and brain trauma will manifest intracranial pressure (ICP) >20 mm Hg. While the pathologic consequences of increased ICP are still being defined, patient outcome after head injury is worse when ICP remains elevated. Management traditionally utilized controlled hyperventilation, fluid restriction, head elevation, diuretics, cerebrospinal fluid drainage, and it was common practice in many neurosurgical ICUs for patients to be managed by a protocol that included routine use of NMB drugs. Paralysis with NMB drugs can effectively prevent or blunt the potent sympathetic and other reflex responses to tracheal suctioning, which will otherwise result in rapid increases in ICP [41]. In addition, of course, NMB drugs facilitate controlled hyperventilation. Despite the efficacy of NMB drugs in facilitating control of intracranial hypertension in patients with head injury, administration of NMB drugs (as part of a routine protocol in trauma ICU patients) has not been documented to improve patient outcome [42]. Hsiang et al. reviewed 514 patients with severe head trauma (Glasgow Coma Scale ≤ 8) collated in the Traumatic Coma Data Bank from 1984 to 1987 [43]. Approximately half these patients received early, and routine, use of NMB drugs, while the other half did not meet these criteria. Patients receiving early, routine use of NMB drugs (Group 1) were characterized by significantly longer ICU stay (8 vs. 5 days), more frequent pneumonia, and a trend towards a higher rate of sepsis [43]. While the mortality was lower in Group 1 patients receiving early NMB drugs (24 percent vs. 39 percent, p < .001), this group also had significantly more vegetative and severely disabled survivors. Significant limitations are inherent in this study, but it raises pertinent questions, and a prospective study is warranted. Currently, the use of NMB drugs

to help control ICP in patients with head trauma remains controversial, as therapeutic priorities in the management of acute head injury continue to evolve.

INDICATIONS AND DRUG SELECTION

Evidence-based information is limited to guide appropriate NMB drug administration in the ICU. A task force of clinicians and other experts from the American College of Critical Care Medicine and the Society of Critical Care Medicine published guidelines in 1995 for use of NMB drugs in the ICU [44]. However, none of the three published recommendations were supported by Level 1 evidence, which was defined as that which would be "convincingly justifiable on scientific evidence alone." In addition, their information and Medline database was limited to that available by 1995, and several new, randomized studies have appeared in the literature since that time (see section on "Prospective Studies of NMB Drugs in the ICU," above). Thus, the opinions expressed below may differ significantly from those of earlier guidelines.

Pharmacodynamic characteristics of current NMB drugs are summarized in Table 4, and are considered in extensive detail elsewhere [13, 45-49]. It is always appropriate, and often sufficient, to maximize sedation and analgesia before consideration of NMB drugs. Many ICU patients may be adequately managed and ventilated with appropriate use of benzodiazepines, propofol and narcotics. When necessary, it is common practice to initiate neuromuscular block with a bolus-loading dose and subsequent infusion of one of the intermediate-duration (cisatracurium, rocuronium) [29, 36, 37] or long-duration (doxacurium, pipecuronium) NMB drugs [38, 39, 50]. These drugs are noteworthy for hemodynamic stability and a duration of action of 0.5-1.5 hours. In renal failure patients or those with multiorgan dysfunction syndrome, cisatracurium exhibits advantages of Hofmann elimination and the lack of active NMB metabolites [40]. Laudanosine production secondary to cisatracurium metabolism is only 20-30 percent of that previously observed with use of atracurium. If a NMB drug with a longer duration of action is desired, doxacurium has proven safe [38, 39]. In addition, because of its long half-life, it may be administered by intermittent bolus or continuous infusion with equal efficacy [38, 39]. In the ICU, drug-drug interactions are common and must also be considered (Table 2). For instance, caution should be exercised in ICU patients receiving therapeutic corticosteroids and concurrent administration of steroid-based NMB drugs. Evidence suggests at least an association between vecuronium or pancuronium, use of exogenous corticosteroids, and subsequent development of prolonged muscle weakness (including "tetraparesis" or "quadraparesis") [5, 10, 34, 51]. In general, the recovery profiles of the steroid-based NMB drugs (rocuronium, vecuronium, pipecuronium, pancuronium) tend to be longer and more variable compared to their benzylisoquinolinium-based counterparts (cisatracurium, atracurium, doxacurium, metocurine) [28, 39]. In any case, it may be prudent to monitor daily CK enzyme levels in patients receiving high-dose steroids and any NMB drug.

The pharmacologic development of tachyphylaxis may be seen in adult or pediatric ICU patients receiving prolonged neuromuscular block, usually within 24 to72 hrs of onset of neuromuscular blockade [52, 53]. Based on speculation and anecdotal evidence, tachyphylaxis may occur more commonly in patients receiving NMB drugs as a continuous infusion, as opposed to intermittent bolus administration. Multiple factors account for tachyphylaxis to NMB drugs in ICU patients, including the proliferation of extrajunctional nACh receptors and an increase in the number of neuromuscular receptor sites [54]. Chronic, partial neuromuscular blockade, similar to partial or complete deafferentation injury, may trigger proliferation of (fetal variant) nACh receptors [18].

Table 4. Pharmacodynamic characteristics of NMB drugs.

Selected Benzylisoquinolinium for ICU use:

	Tubocurarine (Curare)	Cisatracurium (Nimbex)	Atracurium (Tracrium)	Doxacurium (Nuromax)	Mivacurium (Mivacron)
Introduced (yr)	1942	1996	1983	1991	1992
ED_{95} dose (mg/kg)	0.51	0.05	0.25	0.025-0.030	0.075
Initial dose (mg/kg)	0.2-0.3	0.2	0.4-0.5	up to 0.1	0.15-0.25
Duration (min)	80	45-60	25-35	120-150	10-20
Infusion described	?	Yes	Yes	Yes	Yes
Infusion dose (µg/kg/min)	—	2.5-3.0	4-12	0.3-0.5	9-10
Recovery (min)	80-180	90	40-60	120-180	10-20
Renal excretion (%)	40-45	Hoffman elimination	5-10	70	Inactive metabolites
Renal failure	↑	No change	No change	↑ to ↑↑	↑ duration
Biliary excretion (%)	10-40	Hofmann	Minimal	Unclear	—
Hepatic failure	Minimal change to mild	Minimal to no change	Minimal to no change	Minimal change	↑ duration
Active metabolites	No	No	No, but accumulate laudanosine	No	No
Histamine release hypotension	Marked	No	Minimal but dose dependent	none	Minimal but dose dependent
Vagal block tachycardia	Minimal	No	No	No	No
Gaglionic blockade hypotension	Marked	No	Minimal to none	No	No
Prolonged ICU block	?	Rare	Rare	Too early to tell	Too early to tell
Estimated US ICU use	N.R.	Increasing	Minimal	Infrequent	Rare-N.R.
Cost ($) (24-hr estimate)	N.R.	$200-$225	$500	$100-$150	$700

Table 4. Pharmacodynamic characteristics of NMB drugs (continued).

Selected aminosteroids for ICU use:

	Pancuronium (Pavulon)	Vecuronium (Norcuon)	Pipecuronium (Arduan)	Rocuronium (Zemuron)
Introduced (yr)	1972	1984	1991	1994
ED_{95} dose (mg/kg)	0.07	0.05	0.05	0.3
Initial dose (mg/kg)	0.1	0.1	0.085-0.1	0.6-1.0
Duration (min)	90-100	35-45	90-100	30
Infusion described	Yes	Yes	No	Yes
Infusion dose (μg/kg/min)	1-2	1-2	0.5-2.0	10-12
Recovery (min)	120-180	45-60	55-160	20-30
Renal excretion (%)	45-70	50	50+	33
Renal failure	↑ to ↑↑, any metabolites	↑, especially metabolites	↑ duration	minimal
Biliary excretion (%)	10-15	35-50	Minimal	<75
Hepatic failure	Mild ↑ increase	Variable, mild	Minimal	Moderate
Active metabolites	Yes: 3-OH and 17-OH-pancuronium	Yes: 3-desacetyl-veucronium	Not reported	No
Histamine release hypotension	None	None	None	None
Vagal block tachycardia	Modest to marked	No	No	Some at higher doses
Gaglionic blockade hypotension	No	No	No	No
Prolonged ICU block	Yes	Yes	No reports	No reports
Estimated US ICU use	Variable	Decreasing	Uncommon	Variable
Cost ($) (24-hr estimate)	$10	$185-$200	No data	$300

NR, not recommended

Lastly, NMB drugs may constitute a significant fraction of the hospital pharmaceutical budget [15, 16, 55]. The costs associated with NMB drug utilization and prolonged weakness after NMB drugs are increasingly a consideration in drug selection. Costs vary between drugs, and are affected by the mode of administration, bedside monitoring of neuromuscular function and the amount of nursing time required. In addition, occasional patients with unexpected, prolonged muscle weakness will require extended ICU and hospital care, significantly increasing costs. In general, newer drugs (Table 4) are more costly. Older NMB drugs are less expensive, but have less precedent to support their extended use in the ICU. Prolonged weakness or myopathy in the ICU environment may result in many weeks (or even months) of additional ICU care and hospital rehabilitation. A recent economic analysis attempted to quantitate the hospital charges associated with 10 such unfortunate patients. The median additional charges associated with patients who developed prolonged neuromuscular weakness was >$66,000 per patient (excluding rehabilitation), but could reach $200,000 in selected cases [16]. Significant costs were attributed to the requirement for additional mechanical ventilation, neurologic studies, ICU care and hospital days.

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